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Myocardial protection during minimally invasive cardiac surgery through right mini-thoracotomy

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Abstract

Background: Myocardial damage is an independent predictor of adverse outcome following cardiac surgery and myocardial protection is one of the key factors to achieve successful outcomes. Cardioplegia with Custodiol is currently the most used cardioplegia during minimally invasive cardiac surgery (MICS). Different randomized controlled trials compared blood and Custodiol cardioplegia in the context of traditional cardiac surgery. No data are available for MICS.

Aim: The aim of this study was to compare the efficacy of cold blood versus Custodiol cardioplegia during MICS.

Method: We retrospectively evaluated 90 patients undergoing MICS through a right mini-thoracotomy in a three-year period. Myocardial protection was performed using cold blood (44 patients, CBC group) or Custodiol (46 patients, Custodiol group) cardioplegia, based on surgeon preference and complexity of surgery.

Results: The primary outcomes were post-operative cardiac troponin I (cTnI) and creatine kinase MB (CKMB) serum release and the incidence of Low Cardiac Output Syndrome (LCOS). Aortic cross-clamp and cardiopulmonary bypass times were higher in the Custodiol group. No difference was observed in myocardial injury enzyme release (peak cTnI value was 18±46 ng/ml in CBC and 21±37 ng/ml in Custodiol; p=0.245). No differences were observed for mortality, LCOS, atrial or ventricular arrhythmias onset, transfusions, mechanical ventilation time duration, intensive care unit and total hospital stay.

Conclusions: Custodiol and cold blood cardioplegic solutions seem to assure similar myocardial protection in patients undergoing cardiac surgery through a right mini-thoracotomy approach.

Keywords

myocardial protection; minimally invasive cardiac surgery; mini-thoracotomy; cardioplegia; outcomes

Introduction

Cardiac surgery has been evolving at an impressive speed since its birth. Surgical techniques have improved over time in order to provide less invasiveness for the patient, obtaining excellent clinical results and a general approval for their routine application:[1–11] the "minimally invasive" concept was born.

This new concept addressed all the efforts towards the reduction of surgical trauma, resulting in faster recovery with increased patient satisfaction and a reduction of hospital costs.[12–14] The constant evolution of operative field visualization technologies, together with the introduction of new surgical instruments and new methods for cardiopulmonary bypass (CPB) institution, cardioplegia infusion and aortic cross-clamp, led to the diffusion and reproducibility of minimally invasive techniques,[5,15–18] which showed outcomes comparable to standard sternotomy, providing faster recovery, reduced blood product transfusions and cosmetic advantages.[12–14,19]

Nevertheless, minimally invasive cardiac surgery (MICS) is challenging and requires a prolonged learning curve,[20] not only for different surgical exposure, but also

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Table 1. Pre-operative characteristics.

Pre-operative characteristics	CBC (n=44)	Custodiol (n=46)	p-value
Male sex	21 (47.7%)	24 (52.2%)	0.673
Age (years)	54±14	59±14	0.085
Pre-operative LVEF (%)	56±9	57±8	0.669
Hypertension	21 (47.7%)	24 (52.2%)	0.673
Diabetes	1 (2.3%)	1 (2.2%)	1.000
Dyslipidemia	11 (25%)	7 (15.2%)	0.246
CKD	5 (11.4%)	4 (8.7%)	0.737
Atrial Fibrillation	10 (22.7%)	12 (26.1%)	0.711
Pulmonary Hypertension	12 (27.3%)	20 (43.5%)	0.108
Pre-operative cTnI value (ng/ml)	0.03±0.12	0.32±2.08	0.985
Pre-operative CKMB value (ng/ml)	0.9±0.7	2.0±9.9	0.289
Pre-operative AST value (U/L)	24±10	23±16	0.880

Data are expressed as percentages or mean±standard deviation. AST: aspartate aminotransferase; CBC: cold blood cardioplegia; CKD: chronic kidney disease; CKMB: creatine kinase MB; cTnI: cardiac troponin I; LVEF: Left ventricle ejection fraction.

for its intrinsic complexity and the prolonged CPB and aortic cross-clamp times.[21]

CPB is essential to the performance of cardiac surgery, but it entails a systemic inflammatory response syndrome with multiple organ – myocardium included – damage, whose intensity increases with the prolongation of the CPB time.[22] Myocardial damage is an independent predictor of adverse outcome following cardiac surgery[23] and myocardial protection is one of the key factors to achieving successful outcomes.

Cardioplegia with Custodiol is currently the most used cardioplegia during minimally invasive cardiac surgery.[24] Nevertheless, the optimal strategy for myocardial protection is still debated. Two major solutions can be utilized: a blood-based solution with a potassium supplement (blood cardioplegia) and a crystalloid-based solution.[25] Different, randomized, controlled trials (RCTs) compared blood cardioplegia and Custodiol during traditional cardiac surgery[26,27] without providing an unequivocal answer. No data are available for mini-thoracotomy surgery.

The aim of this study was to compare the efficacy of blood cardioplegia versus Custodiol during mini-thoracotomy surgery.

Materials and Methods

Population of the study

Ninety patients undergoing cardiac surgery through right mini-thoracotomy in the Division of Cardiac Surgery of the University of Bari from December 2012 to December 2015 were retrospectively evaluated.

The patients were divided in two groups on the basis of the cardioplegic solution used: the Custodiol cardioplegia (Custodiol™ HTK Bretschneider, dr. Franz Kohler Chemie GMBH, Bensheim, Germany) was used in 46 patients (Custodiol group) while cold blood cardioplegia (CBC), made of blood mixed with St. Thomas No. 2 cardioplegia (Plegisol, Abbott Laboratories, North Chicago, Illinois, USA) in a 4:1 ratio, was used in 44 patients (CBC group). The choice of the cardioplegia was based on surgeon preference and the complexity of the surgery.

The mean age of the patients was 54±14 years in the CBC group and 59±14 years in the Custodiol group (range from 17 to 81 years), with an equal distribution of sexes in both groups (male sex 47.7% CBC group vs 52.2% Custodiol group, p=0.673) (Table 1).

Surgical procedure and operative details

All patients were operated on by two surgeons using the port-access video-assisted technique through a right antero-lateral mini-thoracotomy.

All surgeries were performed using general intravenous anaesthesia with standard protocols and intubation with a double-lumen endotracheal tube for single-lung ventilation. Patients were positioned supine with an air sack under their right scapula in order to elevate the right hemithorax for a better exposition of the operatory field. A 6-7 cm right antero-lateral mini-thoracotomy at the 4th intercostal space was performed; two auxiliary working ports were used for the video assistance and the CO_2 insufflation. After full heparinization (activated clotting time >400s), peripheral (right internal jugular vein, femoral vein and artery) cannulation was performed and CPB was established. The arterial line pressure was maintained <260 mmHg in order to avoid the risk of retrograde dissection; vacuum-assisted venous drainage (VAVD) of −60 mmHg maximum was applied. Proplege (Edwards Lifesciences Corporation, Irvine,

Table 2. Composition of cardioplegic solutions used in the study.

	Custodiol	CBC (First dose)	CBC (Repeated doses)	Unit of measure
NaCl	0.8766	6.63	6.63	g/L
KCl	0.6710	1.22	1.22	g/L
Hexahydrate $MgCl_2$	0.8132	3.35	3.35	g/L
Dihydrate $CaCl_2$	0.0022	0.18	0.18	g/L
$NaHCO_3$	–	0.86	0.86	g/L
Na^+	–	124	124	mEq/L
K^+	–	37.11	20.61	mEq/L
Ca^{++}	–	2.47	2.47	mEq/L
Mg^{++}	–	32.98	32.98	mEq/L
Cl^-	–	164.94	164.94	mEq/L
HCO_3^-	–	10.31	10.31	mEq/L
Hist. chlor. monohydrate	18.0	–	–	mMol/L
Histidine	180.0	–	–	mMol/L
Tryptophan	2.0	–	–	mMol/L
Mannitol	30.0	–	–	mMol/L
Ketoglutarate	1.0	–	–	mMol/L
pH	7.02 – 7.20	7.6 – 8.0	7.6 – 8.0	–

Ca: calcium. $CaCl_2$: calcium chloride; CBC: cold blood cardioplegia; Cl: chlorine; HCO_3: bicarbonate; Hist. chlor.: histidine chlorhydrate; K: potassium; KCl: potassium chloride; Mg: magnesium; $MgCl_2$: magnesium chloride; Na: sodium; NaCl: sodium chloride; $NaHCO_3$: sodium bicarbonate.

CA, USA), a neckline for retrograde cardioplegia infusion, was sometimes positioned.

After CPB institution and aortic cross-clamping, cardiac arrest was induced. The aortic cross-clamping was performed by means of an endoclamp in 37 patients (84.1%) of the CBC group and in 36 patients (78.3%) of the Custodiol group (p=0.480).

In the Custodiol group, the systemic temperature was lowered to 32-34°C. The cardioplegic solution was delivered antegradely with an initial pressure of 80-100 mmHg and a maintenance pressure of 60-70 mmHg after the cardiac arrest; a single dose of 20 ml/kg in at least 6-8 minutes was administered in all patients. Ultrafiltration during CPB was performed in all Custodiol patients.

In the CBC group, systemic temperature was lowered to 34°C. One litre of cold blood cardioplegia with the addition of KCl (20 mEq in the first dose, 4-5 mEq in the following doses) was delivered antegradely (in case of Proplege™ use, 2/3 of the dose was administered antigradely and 1/3 retrogradely) and repeated (about 500 ml) every 20 minutes. A warm blood dose was administered just before cross-clamp removal for reperfusion.

The composition of the cardioplegic solutions used is described in Table 2.

Twenty-two patients underwent isolated mitral valve replacement (MVR) (12 in the CBC group, 10 in the Custodiol group, p=0.541), 39 underwent isolated mitral valve repair (MVRe) (13 in the CBC group and 26 in the Custodiol group, p=0.010), nine underwent MVR combined with tricuspid valve (TV) surgery (four in the CBC group and five in the Custodiol group, p=1.000), seven underwent MVRe combined with TV surgery (three in the CBC group and four in the Custodiol group, p=1.000) and 13 underwent other interventions, which included atrial septal defect (ASD) closure and atrial myxoma removal (12 in the CBC group and one in the Custodiol group, p=0.0001) (Table 3).

Study end-points and statistical analysis

The primary end-point of the study was to evaluate the efficacy of a single dose of Custodiol cardioplegia compared to repeated doses of CBC during right mini-thoracotomy cardiac surgery.

Such assessment was done by measuring myocardial injury enzymes - such as cardiac troponin I (cTnI), creatine kinase MB (CKMB) and aspartate aminotransferase (AST) - serum concentration pre-operatively, eight hours after surgery and on the first and second post-operative days.

Low cardiac output syndrome (LCOS, defined as the need for high dose inotropes and/or mechanical support for more than 24 hours after surgery), atrial and/or ventricular arrhythmias onset incidence, hospital and intensive care unit (ICU) length of stay, number of transfusions and in-hospital mortality rate were evaluated.

Continuous variables were presented as mean±standard deviation. Trends over timing points were displayed by plotting the mean values with standard error. Discrete variables were summarized as frequencies and percentages. Categorical variables were

Table 3. Operative details.

Operative details	CBC (n=44)	Custodiol (n=46)	p-value
MVR	12 (27.3%)	10 (21.7%)	0.541
MVRe	13 (29.5%)	26 (56.5%)	**0.010**
MVR + TV surgery	4 (9.1%)	5 (10.9%)	1.000
MVRe + TV surgery	3 (6.8%)	4 (8.7%)	1.000
Other heart surgery interventions	12 (27.3%)	1 (2.2%)	**0.001**
Surgery (isolated/combined)			
MVRe	17 (38.6%)	31 (67.4%)	**0.006**
MVR	16 (36.4%)	15 (32.6%)	0.708
TVRe	9 (20.5%)	10 (21.7%)	0.881
TVR	1 (2.3%)	0 (0%)	0.489
Myxoma	7 (15.9%)	0 (0%)	**0.005**
ASD	3 (6.8%)	0 (0%)	0.113
Combined surgery	9 (20.5%)	10 (21.7%)	0.881
CPB (min)	129±41	150±50	**0.030**
Cross-clamp (min)	88±30	106±30	**0.006**
Endoclamp	37 (84.1%)	36 (78.3%)	0.480

Data are expressed as percentages or mean±standard deviation. ASD: atrial septal defect; CBC: cold blood cardioplegia; CPB: cardiopulmonary bypass; MVR: mitral valve replacement; MVRe: mitral valve repair; TV: tricuspid valve; TVR: tricuspid valve replacement; TVRe: tricuspid valve repair; Other heart surgery interventions include atrial septal defect closure and atrial myxoma removal.

Table 4. Post-operative details.

Post-operative outcomes	CBC (n=44)	Custodiol (n=46)	p-value
cTnI post 8 h (ng/ml)	14±35	18±37	0.887
CKMB post 8 h (ng/ml)	51±60	68±84	0.667
AST post 8 h (U/L)	110±146	97±97	0.348
cTnI POD (ng/ml)	16±46	15±27	0.899
CKMB POD I (ng/ml)	40±43	54±50	0.615
AST POD I (U/L)	101±103	111±92	0.921
cTnI POD II (ng/ml)	7±21	9±20	0.746
CKMB POD II (ng/ml)	9±9	12±14	0.623
AST POD II (U/L)	73±96	87±70	0.388
Post-operative A/V arrhythmias	14 (32.6%)	14 (30.4%)	0.829
LCOS	4 (9.1%)	3 (6.5%)	0.711
Need for blood transfusions	15 (34.1%)	13 (28.3%)	0.550
Number of RBC units transfused	0.9±1.8	0.9±2.0	0.608
ICU stay (h)	70±214	39±44	0.822
Mechanical ventilation time (h)	46±194	15±35	0.691
Total post-operative hospitalization (days)	9±9	8±3	0.331
Exitus (%)	1 (2.3%)	0 (0%)	0.489

Data are expressed as percentages or mean±standard deviation. POD I/II: first or second post-operative day; A/V: atrial or ventricular; AST: aspartate aminotransferase; CBC: cold blood cardioplegia; CKMB: creatine kinase MB; cTnI: cardiac troponin I; ICU: intensive care unit; LCOS: low cardiac output syndrome; post 8 h: eight hours after surgery; RBC: red blood cells.

compared by use of the $\chi 2$ test or Fisher's exact test, as appropriate. Continuous data were compared by use of the unpaired t test or the Wilcoxon test. To evaluate determinants of post-operative cTnI and CKMB release, a linear regression model was fitted on the post-operative peak-value with cross-clamp duration, cardioplegia, endoclamp and type of surgery as covariates. The cTnI and CKMB had skewed distribution and they were analyzed on log-transformed values. A p-value <0.05 was considered statistically significant. The analyses were made using STATA software, version 14 (StataCorp., College Station, TX, USA).

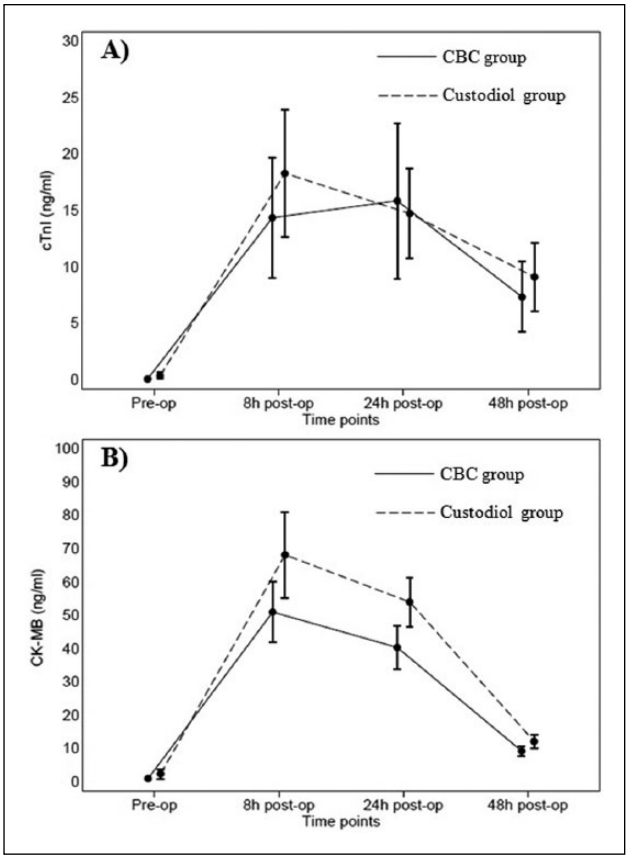

Figure 1. Mean values of cardiac troponin I (cTnI – section A) and creatine kinase MB (CKMB – section B) in both groups (cold blood cardioplegia [CBC] and Custodiol).

Results

Pre-operative characteristics were similar in both groups, with a mean age slightly higher in the Custodiol group (p=0.085) (Table 1).

Mean CPB and cross-clamp times were 129±41 minutes for the CBC group VS 150±50 minutes for the Custodiol group (p=0.030) and 88±30 for the CBC group VS 106±30 minutes for the Custodiol group (p=0.006), respectively (Table 3).

Post-operative data are shown in Table 4. LCOS and atrial/ventricular arrhythmia incidence was similar in the two groups. No statistically significant difference was found for in-hospital mortality rate, mechanical ventilation time and hospital/ICU stay.

cTnI and CKMB serum levels were also similar between the groups (Figure 1). The mean post-operative peaks were 18±46 ng/ml (CBC group) VS 21±47 ng/ml (Custodiol group) for cTnI (p=0.245) and 53±61 ng/ml (CBC group) VS 73±84 ng/ml (Custodiol group) for CKMB (p=0.165).

A multivariate analysis (multiple regression model) was carried out in order to detect the determinants of the markers' post-operative peaks. The most recurrent groups of surgery were included. Considering the MVRe (the most frequent surgery performed on our population) as the landmark, the only factor associated with cTnI (p=0.006) and CKMB (p=0.003) release is cross-clamp time; this effect disappears in the subgroups which are consistent for time and kind (Table 5).

Discussion

Myocardial protection during minimally invasive cardiac surgery via a right mini-thoracotomy has never been specifically studied, maybe because other aspects – such as technical and technological adjustments - of this relatively new kind of surgery were considered more important; moreover, the Custodiol cardioplegia seemed to guarantee excellent results.[28,29]

Our study focused exactly on this barely explored aspect, that is, the myocardial protection during mini-thoracotomy surgery obtained through the administration of two different kind of cardioplegia: one a single-dose crystalloid cardioplegic solution and a multiple-dose cold blood cardioplegic solution at regular intervals.

The multiple-dose cardioplegia might not be the ideal solution for this kind of surgery, especially if the endoclamp is used. Indeed, the endoclamp may be displaced when opening the left atrium, emptying the heart and positioning the atrial retractor. The surgeon is then unable to detect its exact position: he/she runs the risk of excessively pushing forward the balloon, thus, occluding the coronary ostia and causing sub-optimal coronary perfusion because of reduced delivery of the cardioplegic solution. This risk can be avoided by delivering the maintenance doses in the coronary sinus with the specific device. Furthermore, surgeons often tend to prolong the intervals between the maintenance doses in order not to interrupt the surgical action. All of these actions might produce ischaemic periods, which is deleterious for heart cell survival. Therefore, Custodiol cardioplegia use, requiring just a single dose administration, can effectively reduce the occurrence of such a problem.

A single dose of Custodiol cardioplegic solution seems to guarantee long-lasting myocardial protection. The major effects of this cardioplegia are due to histidine, which acts as a buffer and may enhance the efficiency of anaerobic glycolysis, to ketoglutarate, a Krebs Cycle intermediate and the precursor of nicotinamide adenine dinucleotide (NAD), which increases energy creation during reperfusion, to tryptophan, which stabilizes the cellular membrane and to mannitol, which has an anti-oedematous and free radical scavenger effect.[30–32]

In our study, despite longer CPB and cross-clamping times in the Custodiol group, LCOS and myocardial necrosis marker serum release were similar in both groups. This fact may be suggestive of a good reliability of the Custodiol use in the case of prolonged ischaemia

Table 5. Markers' post-operative peaks determinants (Natural Log Scale). Multivariate Analysis.

	cTnI max	p	CK-MB max	p
	β±SE		β±SE	
Groups of surgery				
Isolated MVRe	***Reference point***	**–**	***Reference point***	**–**
Isolated MVR	0.297±0.263	0.263	0.309±0.196	0.118
MV + TV surgery	–0.091±0.310	0.769	0.108±0.231	0.641
Other Surgery	0.064±0.343	0.853	0.055±0.256	0.829
Cross-clamp time (min)	0.011±0.004	**0.006**	0.009±0.003	**0.003**
Endoclamp	–0.110±0.263	0.677	–0.208±0.196	0.291
Custodiol	0.073±0.224	0.746	0.079±0.167	0.636
Isolated MVRe subgroup				
Cross-clamp time (min)	0.007±0.006	0.240	0.009±0.005	0.080
Endoclamp	–0.29±0.328	0.383	–0.404±0.27	0.144
Custodiol	0.561±0.318	0.086	0.315±0.262	0.237
Isolated MVR subgroup				
Cross-clamp time (min)	0.015±0.007	0.065	0.010±0.006	0.088
Endoclamp	0.928±0.803	0.263	0.246±0.612	0.692
Custodiol	–0.686±0.467	0.159	–0.46±0.356	0.212
Combined MV+TV surgery subgroup				
Cross-clamp time (min)	0.001±0.012	0.917	0.002±0.008	0.852
Endo	0.241±0.857	0.783	0.131±0.608	0.832
Custodiol	–0.450±0.575	0.449	–0.039±0.408	0.926
Other surgery subgroup				
Cross-clamp time (min)	0.015±0.014	0.299	0.009±0.008	0.261
Endoclamp	–0.004±0.610	0.994	0.206±0.342	0.561
Custodiol	0.504±1.273	0.702	0.172±0.714	0.815

Data are expressed as regression coefficient±standard error (β±SE). CKMB: creatine kinase MB; cTnI: cardiac troponin I; MV: mitral valve; MVR: mitral valve replacement; MVRe: mitral valve repair; TV: tricuspid valve; Other heart surgery interventions include atrial septal defect closure and atrial myxoma removal.

time. Such a condition induces an overproduction in H^+ ions, thus, limiting anaerobic glycolysis. The histidine contained in Custodiol is able to progressively remove H^+ ions. The consequence is a recovery of the biochemical processes related to anaerobic glycolysis and the related increase in the production of high energy phosphates;[33] moreover, the buffering capacity of such proteins is greater than that of bicarbonate, leading to a better capability to stabilize intracellular pH and prolong myocardial tolerance to global ischaemia.[34] It was also demonstrated that ketoglutarate improves myocardial protection by increasing the oxidative ability.[35,36]

Two major concerns about Custodiol are haemodilution and hyponatraemia[37,38] because of the large volume of crystalloid solution needed to be administered for myocardial protection.[39] Excessive haemodilution may lead to a higher rate of blood transfusions as well as osmolarity alterations. In our group of patients treated with Custodiol, none of such side effects were observed. In fact, no difference in blood transfusion rate or kidney disease was detected. Such findings may be due to the routine utilization of ultrafiltration during CPB in patients receiving this kind of cardioplegia for myocardial protection, leading to a reduced haemodilution.

There are three major limitations in this study: one is its retrospective nature; furthermore, it is a monocentric study with surgery performed by a restricted pool of surgeons on a relatively small number of patients. Lastly, even if the correlation between post-operative cTnI and CKMB serum release and cardiac functional changes has been demonstrated by means of radio-diagnostic methods,[40,41] the study lacks an appropriate instrumental evaluation of post-operative cardiac function.

Even so, in the light of our results, we can assert that Custodiol and cold blood cardioplegia seem to ensure equally satisfying myocardial protection. Further prospective, randomized, controlled trials with an appropriate design are essential to confirm our findings.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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